Title

Biologics May Prevent Cardiovascular Events in Rheumatoid Arthritis by Inhibiting Coronary Plaque Formation and Stabilizing High-Risk Lesions.

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Impact of Cumulative Inflammation, Cardiac Risk Factors, and Medication Exposure on Coronary Atherosclerosis Progression in Rheumatoid Arthritis

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Objective. To explore incidence and progression of coronary atherosclerosis and identify determinants in patients with rheumatoid arthritis (RA). We specifically evaluated the impact of inflammation, cardiac risk factors, duration of medication exposure, and their interactions on coronary plaque progression.

Methods. One hundred one participants with baseline coronary computed tomography angiography findings underwent follow-up assessment a mean ± SD of 83 ± 3.6 months after baseline. Plaque burden was reported as the segment involvement score (describing the number of coronary segments with plaque) and the segment stenosis score (characterizing the cumulative plaque stenosis over all evaluable segments). Plaque composition was classified as noncalcified, mixed, or calcified. Coronary artery calcium (CAC) was quantified using the Agatston method.

Results. Total plaque increased in 48% of patients, and progression was predicted by older age, higher cumulative inflammation, and total prednisone dose ($P < 0.05$). CAC progressors were older, more obese, hypertensive, and had higher cumulative inflammation compared to nonprogressors ($P < 0.05$). Longer exposure to biologics was associated with lower likelihood of noncalcified plaque progression, lesion remodeling, and constrained CAC change in patients without baseline calcification, independent of inflammation, prednisone dose, or statin exposure (all $P < 0.05$). Longer statin treatment further restricted noncalcified plaque progression and attenuated the effect of inflammation on increased plaque and CAC ($P < 0.05$). Stringent systolic blood pressure (BP) control further weakened the effect of inflammation on total plaque progression.

Conclusion. Inflammation was a consistent and independent predictor of coronary atherosclerosis progression in RA. It should therefore be specifically targeted toward mitigating cardiovascular risk. Biologic disease-modifying antirheumatic drugs, statins, and BP control may further constrain plaque progression directly or indirectly.

INTRODUCTION

Individuals with rheumatoid arthritis (RA) experience a higher rate of cardiovascular (CV) events compared to controls (1). We recently reported greater prevalence, severity, burden, and vulnerability of occult coronary plaque in patients with RA compared to age- and sex-matched individuals without autoimmunity (2). Increasing atherosclerosis burden on serial coronary computed tomography (CT) angiography is an independent predictor of acute coronary syndromes in both men and women without autoimmune disease (3,4). In contrast, stabilization in plaque size is associated with decreased risk of future CV events (5). Changes in coronary plaque load and composition in RA are largely unexplored. Two recent studies evaluated determinants of incident coronary artery calcium (CAC) or prevalent CAC progression and described associations with age, higher blood pressure (BP), and triglyceride levels but not with disease-specific traits or treatments (6,7). However, CAC represents ~20% of total plaque burden both in patients with RA and in a general patient population, and may not be present in earlier disease (2,8). More importantly, having additional information on plaque burden and on stenotic severity and composition exclusively obtained by coronary CT angiography significantly improves upon predictive value of CAC for CV events in a general patient population (9).

In the present study, we explored incident coronary plaque rates, prevalent atherosclerosis progression, and changes in plaque composition in patients with RA who underwent coronary CT angiography at baseline and follow-up. We further identified

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determinants of increasing plaque and CAC burden, and specifically investigated the role of cumulative inflammation, cardiac risk factors, RA-specific or ancillary medications, and their interactions on plaque progression. We hypothesized that higher cumulative inflammation may predict greater coronary plaque load at follow-up, and we further posited that duration of exposure to RA-specific medications such as glucocorticoids, conventional synthetic and biologic disease-modifying antirheumatic drugs (DMARDs), traditional cardiac risk factors, and statin treatments may exert opposing effects on plaque growth or composition.

PATIENTS AND METHODS

Patient recruitment. One hundred one patients who participated in a prior coronary CT angiography study of subclinical coronary atherosclerosis in RA (2) underwent follow-up assessments after a mean ± SD of 83 ± 3.6 months. Participants were prospectively followed up at our outpatient rheumatology clinic since their baseline visit (2010–2011). Inclusion and exclusion criteria have been previously described in detail (2). Briefly, patients were enrolled if they met the 2010 American College of Rheumatology/European League Against Rheumatism (EULAR) classification criteria for RA (10), were ≥18 years of age, and had no symptoms or history of CV disease at baseline. Major exclusion criteria were concomitant autoimmune syndromes (with the exception of Sjögren's syndrome), weight >325 pounds (147.7 kg), iodine allergy, glomerular filtration rate <60 ml/minute, malignancy, and chronic or active infections. The study was approved by the local institutional review board, and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Predictor variables. Hypertension was defined as a systolic BP of ≥140 mm Hg or a diastolic BP of ≥90 mm Hg, or the use of an antihypertensive agent. Diabetes mellitus was defined as a glycosylated hemoglobin level of >6.5% or hypoglycemic medication use. Hyperlipidemia was defined as a fasting cholesterol level of >200 mg/dl, a low-density lipoprotein (LDL) level of >130 mg/dl, or statin use. Smoking was defined as cigarette consumption within 30 days from screening. The waist-to-height ratio was used to measure LDL central obesity (11). Screening for incident cardiac risk factors was conducted in accordance with the EULAR recommendations for CV risk assessment (12). Disease activity was evaluated using the Disease Activity Score in 28 joints (13) using the C-reactive protein level (DAS28-CRP) at every clinic visit. Cumulative inflammatory burden was calculated as a time-averaged CRP spanning all visits between baseline and follow-up scans (14). Medications were reconciled at every clinic visit, including use and doses of prednisone, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs, and statins. Total prednisone and methotrexate doses from baseline to follow-up were calculated, and the number of years of exposure to biologic DMARDs and statins were also estimated.

Laboratory evaluations. A complete blood cell count, comprehensive metabolic panels, erythrocyte sedimentation rate (ESR), and CRP levels were calculated on the day of each coronary CT angiography assessment, as well as at every clinic visit between scans. Fasting lipid evaluations were performed on the day of each scan, in accordance with the EULAR recommendations for CV risk assessment between scans (12).

Multidetector coronary CT angiography. Baseline scans were performed using a 64-multidetector row LightSpeed VCT scanner (GE Healthcare) between March 2010 and March 2011. Follow-up scans were performed using a 256-multidetector row scanner between March 2017 and March 2018. Baseline and follow-up images were analyzed in the same campaign and in random order by a single, blinded interpreter (MJB) (15). CAC was quantified by the Agatston method (16). Coronary arteries were evaluated on contrast-enhanced scans using a standardized 17-segment American Heart Association model (17). For longitudinal comparisons, baseline and follow-up coronary segments were coaligned using fixed anatomic landmarks as fiducial points. Each segment was scored for stenosis severity on a 0–4 scale based on grade of luminal restriction, where 0 = 0% (absence of plaque), 1 = 1–29% stenosis, 2 = 30–49% stenosis, 3 = 50–69% stenosis, and 4 = >70% stenosis (2). Plaque composition was defined as noncalcified, mixed, or calcified as previously reported (18). Subjects received 2 individual quantitative scores; the segment involvement score represented the total number of segments with plaque, and the segment stenosis score described the cumulative stenosis grade rendered by plaque in all evaluable segments. Reproducibility of these scoring measures at our institution has been previously reported (18).

Outcome measures. Changes in burden of total plaque, specific plaque types (noncalcified, mixed, and calcified), and CAC constituted the primary outcome measures. Atherosclerosis progression was defined as the number of new segments with any plaque per patient (segment involvement score increase, possible range 0–17) or rise in stenotic plaque severity in all evaluable coronary segments with plaque (segment stenosis score increase, possible range 0–68). CAC progression was expressed as the absolute difference between the follow-up measurement and the baseline measurement of CAC.

Statistical analysis. Continuous variables were expressed as the mean ± SD, and categorical variables were expressed as the number and percentage. Negative binomial regression was used to assess continuous outcome measures (segment involvement score increase and segment stenosis score increase), robust logistic regression was used to assess categorical outcome measures (noncalcified, mixed, and calcified plaque progression), and generalized linear models with a Tweedie (Poisson-Gamma) error distribution and log link function were used to assess CAC change.

For each outcome measure, univariable models with candidate predictors were estimated, followed by multivariable models constructed via a backward elimination variable selection process. The backward selection process started with all predictors associated with the outcome in univariable analyses at a P value of < 0.20 and sequentially removed variables with a P value of >0.10, beginning with the least significant variable. For primary outcome measures, the possible presence of interactions between cumulative inflammation and traditional risk factors was tested by introducing into the adjusted multivariable models the product of time-averaged CRP and each CV risk factor, and the product of time-averaged CRP and each medication exposure variable. Age and time between scans were included as covariates in all models. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated. Analyses were performed using SPSS software.

RESULTS

Participants were predominantly female with established, seropositive, erosive, and well-controlled disease (Table 1). Follow-up included an average of 19 visits over 7 years. Forty-eight patients were considered plaque progressors based on either

Table 1. Baseline clinical characteristics of progressors versus nonprogressors*

	No plaque progression (n = 53)	Plaque progression (n = 48)	Total sample (n = 101)
Age, years	48.07 ± 9.88	55.19 ± 9.49†	51.45 ± 10.29
Female, no. (%)	46 (86.79)	41 (85.42)	87 (86.14)
Follow-up duration, years	7.00 ± 0.33	6.94 ± 0.34	6.97 ± 0.33
No. of visits	18.83 ± 3.49	18.46 ± 4.18	18.65 ± 3.82
RA-related parameters			
RA duration, years	9.18 ± 6.28	11.36 ± 7.98	10.22 ± 7.19
RF-positive, no. (%)	48 (90.57)	43 (89.58)	91 (90.10)
ACPA-positive, no. (%)	47 (88.68)	40 (83.33)	87 (86.14)
Erosions, no. (%)	33 (62.26)	31 (64.58)	64 (63.37)
Time-averaged CRP, mg/dl	0.79 ± 0.53	0.99 ± 1.16	0.89 ± 0.89
Time-averaged SJC	1.83 ± 1.92	2.40 ± 2.84	2.10 ± 2.41
Time-averaged DAS28-CRP	2.69 ± 0.80	2.70 ± 0.90	2.69 ± 0.84
Cardiovascular risk factors			
Hypertension at baseline, no. (%)	16 (30.19)	29 (60.42)†	45 (44.55)
Time-averaged systolic BP, mm Hg	127.83 ± 13.11	133.08 ± 11.41†	130.32 ± 12.55
Time-averaged diastolic BP, mm Hg	71.97 ± 7.05	72.21 ± 6.56	72.08 ± 6.79
Dyslipidemia at baseline, no. (%)	25 (47.17)	26 (54.17)	51 (50.50)
Time-averaged LDL, mg/dl	101.78 ± 23.38	109.84 ± 35.30	105.61 ± 29.77
Diabetes at baseline, no. (%)	5 (9.43)	9 (18.75)	14 (13.86)
Current smoking, no. (%)	4 (7.55)	4 (8.33)	8 (7.92)
Waist-to-height ratio	57.82 ± 6.83	61.20 ± 7.78†	59.42 ± 7.46
Medication at baseline			
Prednisone use, no. (%)	12 (22.64)	19 (39.58)	31 (30.69)
No. of concomitant csDMARDs	1.90 ± 0.78	1.87 ± 0.79	1.89 ± 0.78
Biologic DMARD use, no. (%)	34 (64.15)	30 (62.50)	64 (63.37)
Statin use at baseline, no. (%)	20 (37.74)	21 (43.75)	41 (40.59)
Medication during follow-up			
Cumulative prednisone, gm‡	2.34 ± 4.49	4.12 ± 6.35	3.19 ± 5.50
Cumulative methotrexate, gm	36.01 ± 18.04	38.81 ± 18.52	37.34 ± 18.23
Biologic DMARD duration, years§	4.36 ± 2.88	4.24 ± 3.01	4.30 ± 2.93
Statin duration, years¶	1.83 ± 2.58	3.04 ± 2.82†	2.41 ± 2.75
Baseline plaque burden			
Total segment involvement score	0.94 ± 0.97	2.88 ± 2.76†	1.86 ± 2.24
Total segment stenosis score	1.04 ± 1.11	4.46 ± 5.11†	2.66 ± 3.98
Noncalcified plaque >0, no. (%)	29 (54.72)	31 (64.58)	60 (59.41)
Mixed plaque >0, no. (%)	4 (7.55)	20 (41.67)†	24 (23.76)
Calcified plaque >0, no. (%)	3 (5.66)	16 (33.33)†	19 (18.81)
CAC >0, no. (%)	5 (9.43)	26 (54.17)†	31 (30.69)
Agatston score	8.85 ± 53.49	135.29 ± 397.36†	68.94 ± 282.35

* Except where indicated otherwise, values are the mean ± SD. RA = rheumatoid arthritis; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody; CRP = C-reactive protein; SJC = swollen joint count; DAS28 = Disease Activity Score in 28 joints; BP = blood pressure; LDL = low-density lipoprotein; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; CAC = coronary artery calcium.
† P < 0.05 versus nonprogressors.
‡ Patients (n = 49) exposed to prednisone at any time between baseline and follow-up scans.
§ Patients (n = 78) exposed to biologic DMARDs at any time between baseline and follow-up scans.
¶ Patients (n = 59) exposed to statins at any time between baseline and follow-up scans.

displaying new coronary segments with plaque (segment involvement score change, range 0–6 among all patients) or increased stenotic severity in segments with prior plaque (segment stenosis score change, range 0–9 among all patients). Clinical characteristics of progressors and nonprogressors are presented in Table 1. RA-related parameters and treatments were similarly distributed across both groups, including use of csDMARDs, time receiving biologic DMARDs, and total prednisone and methotrexate doses. Although progressors were older, more obese, more likely to have hypertension, and had a higher time-averaged systolic BP compared to nonprogressors, those differences were no longer significant after adjustment for age. Progressors more commonly had plaque and CAC, as well as higher plaque and CAC scores at baseline ($P < 0.05$). Eight incident CV events (4 ischemic and 4 nonischemic) occurred throughout the observation period (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41122/abstract). All patients with CV events remained in the study and were included in the analysis.

Incident plaque rates, plaque progression, and calcification over time. Seventy patients (69.3%) displayed coronary plaque at baseline. The rate of incident plaque (segment involvement score >0 at follow-up in patients with a baseline segment involvement score of 0), was 4.7/100 person-years (95% CI 2.2–8.6); in patients with prevalent atherosclerosis (baseline segment involvement score >0), plaque progressed at a rate of 7.8/100 person-years (95% CI 5.5–10.7). The rate of CAC progression was 6.0/100 person-years (95% CI 4.3–8.1); it increased at a median of 15.1 Agatston units/year in patients with prevalent CAC (95% CI 9.3–32.6). Patients with incident CAC demonstrated a median annualized progression rate of 1.7 units (95% CI 0.8–4.1). Quantitative changes for total plaque as well as all 3 plaque subtypes are shown in Supplementary Table 2 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41122/abstract). Overall, total plaque burden and coronary calcification scores increased ($P \leq 0.012$); additionally, progression of noncalcified plaque occurred in 9 patients, mixed plaque in 21, and calcified plaque in 35.

Changes in coronary plaque composition. At baseline, 187 coronary segments with plaque were identified in 70 patients. At follow-up, 97 new lesions appeared in segments without plaque initially; 15 new plaques were identified in 10 patients (9.9%) without plaque at baseline, while 82 new plaques were identified in 37 patients (36.6%) with prevalent plaque. Of the 97 incident plaques reported at follow-up, 20 were noncalcified, 21 were mixed, and 56 were calcified. Figure 1 delineates per-plaque composition changes from baseline to follow-up.

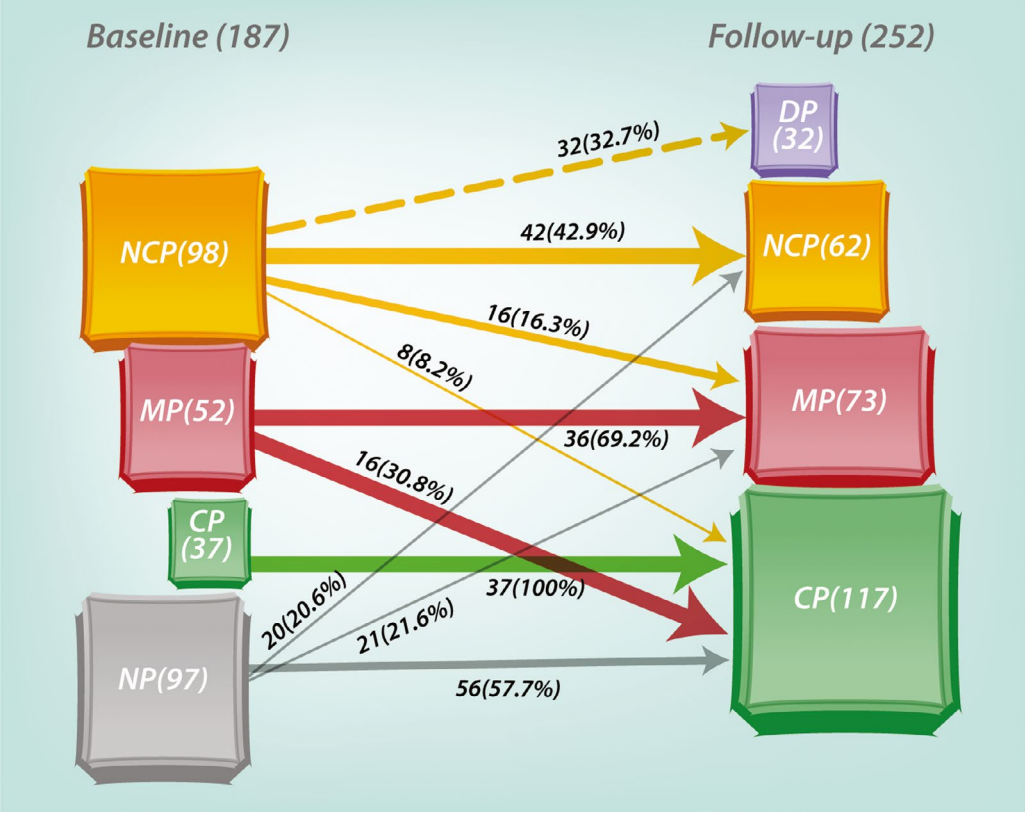

Figure 1. Change in plaque composition, new plaque (NP), and disappearing plaque (DP) from baseline to follow-up. NCP = noncalcified plaque; MP = mixed plaque; CP = calcified plaque.

Table 2. Predictors of total coronary plaque progression in patients with rheumatoid arthritis*

	Segment involvement score increase, estimate (95% CI)		Segment stenosis score increase, estimate (95% CI)		CAC increase, estimate (95% CI)	
	Univariable model	Multivariable model	Univariable model	Multivariable model	Univariable model	Multivariable model
Age, years	–	1.06 (1.03–1.09)†	–	1.05 (1.02–1.08)‡	–	1.17 (1.09–1.26)†
Male sex	1.05 (0.38–2.90)	–	1.04 (0.43–2.52)	–	1.05 (0.38–2.90)	–
Hypertension	1.74 (0.92–3.31)§	–	1.61 (0.90–2.90)	–	2.54 (1.19–5.42)‡	2.58 (0.99–6.78)§
Dyslipidemia	0.74 (0.41–1.33)	–	0.94 (0.54–1.62)	–	1.17 (0.59–2.32)	–
Diabetes	1.06 (0.45–2.51)	–	1.36 (0.63–2.94)	–	0.96 (0.39–2.37)	–
Waist-to-height ratio	1.03 (1.00–1.07)§	–	1.02 (0.98–1.06)	–	1.07 (1.03–1.11)‡	1.17 (1.02–1.34)¶
Time-averaged CRP, mg/dl	1.64 (1.36–1.98)†	1.42 (1.13–1.78)‡	1.52 (1.23–1.88)†	1.35 (1.08–1.70)‡	1.65 (1.34-2.03)†	1.64 (1.14–2.35)‡
Statin duration, years	1.05 (0.95–1.16)	–	1.04 (0.94–1.15)	–	1.14 (1.03–1.26)‡	–
Biologic DMARD duration, years	1.05 (0.97–1.14)	–	1.03 (0.94–1.12)	–	1.09 (0.96–1.23)	–
Cumulative methotrexate, gm	1.01 (0.99–1.02)	–	1.00 (0.99–1.02)	–	1.01 (0.99–1.03)	–
Cumulative prednisone, gm	1.09 (1.05–1.13)†	1.06 (1.02–1.10)‡	1.08 (1.05–1.12)†	1.06 (1.02–1.10)‡	1.07 (1.04–1.11)†	1.10 (1.01–1.21)¶

* 95% = 95% confidence interval; CAC = coronary artery calcium; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug.
† $P < 0.001$.
‡ $P < 0.01$.
§ $P < 0.1$.
¶ $P < 0.05$.

Determinants of change in coronary atherosclerosis burden. Older age, higher time-averaged CRP, and greater total prednisone dose independently predicted both segment involvement score increase and segment stenosis score increase in multivariate models (Table 2). The effect of time-averaged CRP on total plaque increase was modified by statin use, since time-averaged CRP predicted segment involvement score increase only in patients who were not exposed to statins

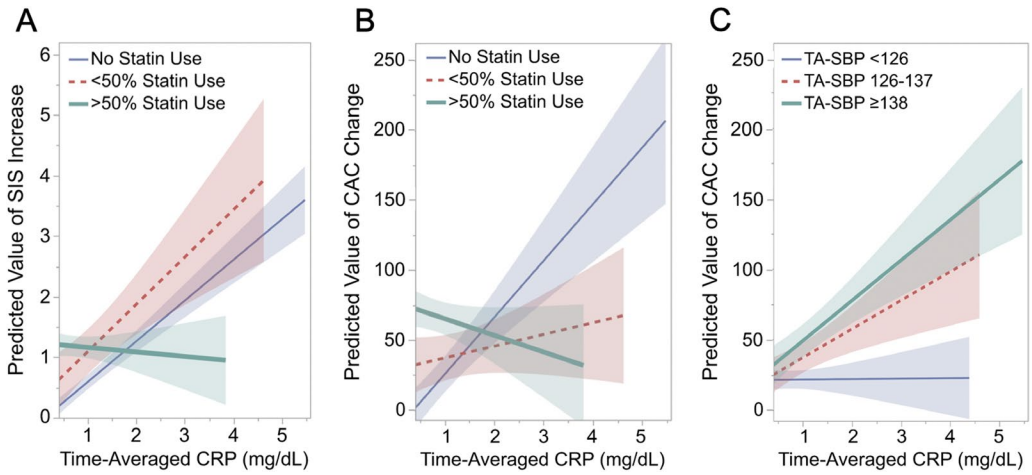

Figure 2. Duration of statin exposure and blood pressure control moderate the effect of cumulative inflammation on coronary plaque progression in rheumatoid arthritis. Relative risks (RRs) and odds ratios (ORs), with 95% confidence intervals (95% CIs), were calculated. **A**, Higher time-averaged C-reactive protein (CRP) yielded significant plaque progression in patients not receiving statins (RR 1.48 [95% CI 1.05–2.09], $P = 0.025$) and those receiving statins for <50% of the study period (RR 1.31 [95% CI 1.01–1.69], $P = 0.040$). No such risk was observed in patients with statin exposure for >50% of the study period (RR 1.07 [95% CI 0.93–1.22], $P = 0.35$, P for interaction = 0.017). **B**, Higher time-averaged CRP rendered high coronary artery calcium (CAC) progression risk in statin-naïve patients (OR 2.33 [95% CI 1.29–4.22], $P = 0.005$); in contrast, any statin exposure mitigated that risk (OR 1.17 [95% CI 0.81–1.68], $P = 0.410$; $P = 0.98$ for statin exposure <50% and OR 0.96 [95% CI 0.44–2.17], $P = 0.98$ for statin exposure >50%; P for interaction = 0.006). Both statin interaction models reported in **A** and **B** are adjusted for age, dyslipidemia, cumulative prednisone dose, total methotrexate dose, and biologic disease-modifying antirheumatic drug treatment duration. **C**, Higher time-averaged CRP significantly predicted CAC progression in patients in the middle and highest tertiles of time-averaged systolic blood pressure (TA-SBP) (OR 1.68 [95% CI 1.14–2.47], $P = 0.009$ and OR 2.39 [95% CI 1.52–3.77], $P < 0.001$, respectively), but not those in the lowest tertile (OR 1.03 [95% CI 0.61–1.74], $P = 0.92$). SIS = segment involvement score.

Table 3. Predictors of change in atherosclerosis burden by plaque type in patients with rheumatoid arthritis*

	Noncalcified plaque progression, OR (95% CI)		Mixed plaque progression, OR (95% CI)		Calcified plaque progression, OR (95% CI)	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Age, years	–	1.00 (0.93–1.07)	–	1.06 (1.00–1.12)†	–	1.18 (1.09–1.27)‡
Male sex	1.17 (0.18–7.73)	–	1.34 (0.39–4.59)	–	1.78 (0.28–11.23)	–
Hypertension	0.25 (0.03–2.11)	–	1.68 (0.56–5.02)	–	4.30 (1.55–11.96)§	3.53 (1.00–12.53)¶
Dyslipidemia	0.40 (0.09–1.88)	–	0.50 (0.17–1.43)	–	1.49 (0.56–3.95)	–
Diabetes	0.72 (0.07–7.18)	–	1.36 (0.36–5.17)	–	2.42 (0.81–7.27)	–
Waist-height ratio	0.92 (0.82–1.04)	–	1.06 (0.99–1.13)	–	1.15 (1.08–1.22)‡	1.16 (1.07–1.25)‡
Time-averaged CRP, mg/dl	1.09 (0.64–1.87)	–	0.70 (0.24–2.02)	–	3.12 (1.92–5.05)‡	3.42 (1.85–6.35)‡
Statin duration, years	0.69 (0.55–0.88)§	0.72 (0.57–0.90)§	1.14 (0.94–1.39)	–	1.10 (0.93–1.31)	–
Biologic DMARD duration, years	0.76 (0.60–0.96)†	0.77 (0.61–0.98)†	1.12 (0.93–1.34)	–	1.07 (0.92–1.25)	–
Cumulative methotrexate, gm	1.03 (0.99–1.08)	–	1.01 (0.98–1.04)	–	1.00 (0.97–1.03)	–
Cumulative prednisone, gm	0.99 (0.92–1.07)	–	1.05 (0.96–1.13)	–	1.08 (0.99–1.18)¶	–

* Model 1 was adjusted for age and time between scans. Model 2 was adjusted as in model 1, and additionally for all variables in the final multivariable model selected using backward selection. OR = odds ratio; 95% CI = 95% confidence interval; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug.
† $P < 0.05$.
‡ $P < 0.001$.
§ $P < 0.01$.
¶ $P < 0.1$.

or received statins for <50% of the study period, but not in those who received statins >50% of the time (P for interaction = 0.017) (Figure 2A).

CAC change was independently predicted by age, obesity, time-averaged CRP, and total prednisone dose (Table 2). Statin exposure also modified the effect of time-averaged CRP on CAC change. Specifically, higher time-averaged CRP was significantly associated with CAC change only in patients not exposed to statins, but not in patients who had any statin exposure during the study period (P for interaction = 0.006) (Figure 2B). Additionally, the effect of time-averaged CRP on CAC change was moderated by time-averaged systolic BP; specifically, time-averaged CRP significantly predicted CAC change in patients in the middle tertile (time-averaged systolic BP 126–137 mm Hg) and highest tertile (time-averaged systolic BP ≥138 mm Hg), but not those in the lowest tertile of time-averaged systolic BP (P for interaction = 0.023) (Figure 2C).

CAC change was further assessed separately in patients with and those without detectable baseline CAC in a supplementary analysis, due to a significant interaction between baseline CAC and duration of biologic DMARD treatment (P for interaction = 0.001). In a model with adjustment for age, obesity, time-averaged CRP, and total prednisone dose, longer biologic DMARD exposure was negatively associated with CAC change in patients without CAC at baseline (OR 0.77 [95% CI 0.60–0.98]; $P = 0.031$), but not in those with prevalent CAC (OR 1.08 [95% CI 0.94–1.23]; $P = 0.28$). The presence of CAC at baseline did not modify the effects of the other primary predictors on CAC change (data not shown).

Determinants of plaque progression by subtype (noncalcified, mixed, calcified) are displayed in Table 3. Both a longer duration of biologic DMARD treatment and exposure to statins were independently associated with a decreased likelihood of noncalcified plaque progression. Inclusion of total prednisone and methotrexate dose in the model did not affect the results (data not shown). Older age was associated with both mixed plaque and calcified plaque progression. Increased calcified plaque burden was further associated with obesity and higher cumulative inflammation.

DISCUSSION

This is the first study to explore predictors of coronary plaque progression in a well-characterized, prospective cohort of patients with RA without known CV disease and with long-term follow-up. We specifically investigated the effects of cumulative inflammation, traditional cardiac risk factors, RA-specific and ancillary therapies and their interactions on total plaque progression, various plaque subtypes, and coronary calcification. Our findings complement previous reports on CAC progression in RA (6,7).

We report several novel findings. First, higher cumulative inflammation was a consistent and independent predictor of total coronary plaque progression in RA. This included new segments with plaque at follow-up, as well as greater stenosis severity in segments with plaque at baseline. This is consistent with 2 previous studies showing that higher inflammatory burden was associated with carotid plaque progression in RA (19,20). However, our observation is of unique significance, since the presence of carotid plaque in inflammatory joint diseases (including

RA) does not sufficiently identify patients with coronary artery disease and since quantitative measurements of carotid atherosclerosis do not correlate with the presence or burden of coronary plaque (21). We used time-averaged CRP as a surrogate for cumulative inflammation; in supplementary analyses, similar results were observed using time-averaged swollen joint counts as a predictor, but not when time-averaged tender joint counts, time-averaged patient global assessments, or composite indices such as the DAS28-CRP or the Clinical Disease Activity Index (22) were used. Importantly, higher cumulative inflammation in RA has been associated with a greater risk of a future CV event (23), while reduction in time-averaged inflammation yielded a lower risk of a CV event (24). Since atherosclerosis progression on serial coronary CT angiography independently predicted CV events in a general patient population (3,5), our observations collectively reaffirm that stringent and durable control of inflammation should be a primary objective in the quest to mitigate CV risk in RA.

Second, higher cumulative inflammation may also promote plaque remodeling and maturation, as evidenced by its strong association with CAC and calcified plaque progression. Indeed, 56 of 117 segments (48%) with calcified plaque at follow-up had no plaque at baseline. Ostensibly, incident plaques appeared in those segments as noncalcified plaques that grew and matured over periods of inflammation during disease flares; as inflammation subsided, they eventually transitioned to advanced, heavily calcified plaques. Support for this timeline was provided by supplementary analyses, where we demonstrated that the within-patient variability in CRP over time significantly predicted CAC progression independent of age, hypertension, obesity, and baseline CAC ($P = 0.018$). In accordance with this, previous reports confirmed that early atherogenesis inflammation drives and colocalizes with initial intimal calcification (25). In response to proinflammatory cytokine production by macrophages at sites of lipid accumulation, vascular smooth muscle cells (VSMCs) undergo apoptosis, release extracellular vesicles secondary to stress, or undergo phenotype transition to osteoblastic cells as a self-preservation strategy. All those events are associated with local calcification, which is initially undetectable using coronary CT angiography (25). If inflammation persists, macrophage infiltration and microcalcifications progress, eventually appearing as spotty calcifications on coronary CT angiography. If inflammation subsides and the VSMC repair system is not overwhelmed (cells do not die by apoptosis in the meantime), this process will lead to the development of calcified acellular plaque.

In advanced plaque, large, dense calcifications are spatially distinct from macrophages, inversely correlate with macrophage burden, and—like the calcific mummification of soft tissue infections—represent healing that stabilizes the arterial wall (25). Hence, higher burden of calcified plaque at follow-up may reflect the final stage in the plaque life cycle that appeared and evolved in the context of a historically higher inflammatory load. However, this association between inflammation and calcification was not observed in prior studies of CAC progression in RA (6,7). Potential explanations may be the longer duration of follow-up (7 years compared to ≤3 years) and greater number of evaluation points (19 compared to 2 or 3) in our study, allowing for a more comprehensive assessment of inflammation variability as well as adequate time for plaque remodeling.

Our third novel finding is that longer biologic DMARD exposure may yield an atheroprotective effect in RA, independent of stringent control of systemic inflammation. Specifically, lengthier biologic DMARD treatment reduced the likelihood of noncalcified plaque progression, the earliest histologic atherosclerotic lesion discernible on coronary CT angiography. Biologic therapies were similarly shown to selectively influence lipid-rich, soft plaque volume in patients with psoriasis (26). Moreover, we showed that lengthier biologic DMARD exposure appeared to prevent maturation and remodeling of such plaques, as evidenced by the lower risk of progressive calcification independent of inflammation, duration of statin exposure, and total prednisone dose. In a similar manner, biologic DMARDs have been shown to inhibit radiographic progression in RA regardless of attainment of optimal disease control (27–29). In contrast, neither duration of exposure to csDMARDs nor total methotrexate dose in our study influenced coronary plaque progression.

Fourth, we established an independent coronary atheroprotective effect of statins in RA. Longer statin exposure was associated with lower risk of noncalcified plaque progression regardless of cumulative inflammation, total prednisone and methotrexate dose, or biologic DMARD duration. Indeed, stabilization or reduction in plaque size, particularly the noncalcified lipid core component, is well documented in response to high intensity statin therapy in general patient populations (30–33) and related to lower risk of CV events (5). However, the atheroprotective effect of statin in our study was not related to the treatment intensity, but rather the duration of the exposure. Our additional observation that the duration of statin exposure moderated the effect of cumulative inflammation on both plaque and CAC progression highlights potential local antiinflammatory effects of statins at the plaque level (34), independent of systemic inflammation as reflected by blood CRP levels (35).

Regrettably, sustained remission may be unrealistic for the majority of patients at the present time (36). Could RA-specific or other ancillary treatments mitigate coronary plaque progression in subjects who do not achieve stringent inflammation control? We observed that longer statin exposure also moderated the effect of inflammation on total plaque progression. In patients treated with statins for >50% of the observation time, higher time-averaged CRP failed to yield significant progression of either coronary plaque or CAC. We further noted that durable, aggressive systolic BP control throughout the observation period may be instrumental, particularly in the setting of chronic residual

inflammation. Time-averaged systolic BP at the lowest tertile (<126 mm Hg) attenuated the effect of higher cumulative inflammation on CAC progression, whereas higher measurements significantly accelerated it. Nevertheless, it is presently unclear whether atheroprotection in RA—specifically in the context of residual inflammation—requires adjustment of the recommendations for starting lipid-lowering therapy or adoption of more rigorous systolic BP targets than in general patient populations (37).

We also demonstrated that cumulative prednisone dose adversely affected total coronary plaque as well as CAC progression, independent of cumulative inflammation or cardiac risk factors. Despite the fact that physicians generally prescribe glucocorticoids to patients with higher disease activity, our observations highlight the true deleterious effect of glucocorticoids on the vascular wall, rather than confounding by indication. Importantly, the duration of statin exposure in our study did not moderate the effect of total prednisone dose on coronary plaque progression, as previously reported for carotid atherosclerosis (19). Since a higher cumulative prednisone dose has been linked to a greater incidence of CV events in RA (38), timely tapering and withdrawal may be warranted.

Our study has certain limitations. First, the absence of a control group hinders the ability to determine whether the observed magnitude and predictors of plaque change in RA are different from those in subjects without autoimmunity. However, at least for CAC, where there is a precedent for comparison (39), the observed CAC progression in our patients was significantly higher than predicted based on age, sex, and ethnicity-matched reference values (relative risk 2.21 [95% CI 1.39–3.52], $P = 0.001$). Second, our patients had low cumulative inflammatory burden; 47% had a time-averaged DAS28-CRP of <2.4, and 68% had a DAS28-CRP of <2.8. Moreover, all patients received rigorous screening and management of incident cardiac risk factors during their clinic visits. Additionally, patients with prevalent calcification or significant plaque burden on baseline coronary CT angiography received at least statin therapy, if not more aggressive treatment, for atherosclerosis, regardless of the presence or absence of clinical symptoms. Consequently, the likelihood of plaque progression may have been attenuated in patients who would otherwise have exhibited the greatest increase. Accordingly, the proportions, magnitude of plaque progression, and effect sizes of predictors may have been attenuated, compared to cohorts with higher disease activity or untreated risk factors.

Occult coronary atherosclerosis burden increased in a significant proportion of patients with RA. Cumulative inflammatory burden and total prednisone dose were disease-specific, independent determinants of plaque progression. Our findings confirm the importance of prioritizing and targeting durable control of inflammation in RA. Longer exposure to biologic DMARDs or statins, as well as rigorous control of systolic BP, may further moderate the effect of inflammation on atherosclerosis progression and yield additional coronary atheroprotective effects beyond optimal control of systemic inflammation.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content and all authors approved the final version to be published. Dr. Karpouzas had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Naranjo A, Sokka T, Descalzo MA, Calvo-Alén J, Hørslev-Petersen K, Luukkainen RK, et al, and the QUEST-RA Group. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther 2008;10:R30.
2. Karpouzas GA, Malpeso J, Choi TY, Li D, Munoz S, Budoff MJ. Prevalence, extent and composition of coronary plaque in patients with rheumatoid arthritis without symptoms or prior diagnosis of coronary artery disease. Ann Rheum Dis 2014;73:1797–804.
3. Motoyama S, Ito H, Sarai M, Kondo T, Kawai H, Nagahara Y, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol 2015;66:337–46.
4. Gu H, Gao Y, Wang H, Hou Z, Han L, Wang X, et al. Sex differences in coronary atherosclerosis progression and major adverse cardiac events in patients with suspected coronary artery disease. J Cardiovasc Comput Tomogr 2017;11:367–72.
5. Inoue K, Motoyama S, Sarai M, Sato T, Harigaya H, Hara T, et al. Serial coronary CT angiography-verified changes in plaque characteristics as an end point: evaluation of effect of statin intervention. JACC Cardiovasc Imaging 2010;3:691–8.
6. Chung CP, Giles JT, Kronmal RA, Post WS, Gelber AC, Petri M, et al. Progression of coronary artery atherosclerosis in rheumatoid arthritis: comparison with participants from the Multi-Ethnic Study of Atherosclerosis. Arthritis Res Ther 2013;15:R134.
7. Udachkina HV, Novikova DS, Popkova TV, Kirillova IG, Markelova EI. Dynamic of changes in coronary artery calcification in early rheumatoid arthritis patients over 18 months. Rheumatol Int 2018;38:1217–24.
8. Leschka S, Seitun S, Dettmer M, Baumüller S, Stolzmann P, Goetti R, et al. Ex vivo evaluation of coronary atherosclerotic plaques: characterization with dual-source CT in comparison with histopathology. J Cardiovasc Comput Tomogr 2010;4:301–8.
9. Hou ZH, Lu B, Gao Y, Jiang SL, Wang Y, Li W, et al. Prognostic value of coronary CT angiography and calcium score for major adverse cardiac events in outpatients. JACC Cardiovasc Imaging 2012;5:990–9.
10. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American

College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.

11. Swainson MG, Batterham AM, Tsakirides C, Rutherford ZH, Hind K. Prediction of whole-body fat percentage and visceral adipose tissue mass from five anthropometric variables. PloS One 2017;12:e0177175.
12. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010;69:325–31.
13. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
14. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ 1990;300:230–5.
15. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol 2008;52:1724–32.
16. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
17. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2014;8:342–58.
18. Pagali SR, Madaj P, Gupta M, Nair S, Hamirani YS, Min JK, et al. Interobserver variations of plaque severity score and segment stenosis score in coronary arteries using 64 slice multidetector computed tomography: a substudy of the ACCURACY trial. J Cardiovasc Comput Tomogr 2010;4:312–8.
19. Giles JT, Post WS, Blumenthal RS, Polak J, Petri M, Gelber AC, et al. Longitudinal predictors of progression of carotid atherosclerosis in rheumatoid arthritis. Arthritis Rheum 2011;63:3216–25.
20. Im CH, Kwon SH, Eun JS, Kim NR, Nam EJ, Kang YM. Inflammatory burden predicts carotid plaque progression and subsequent cardiovascular events in rheumatoid arthritis: the 2-year prospective cohort study [abstract]. Arthritis Rheum 2013;65:S155.
21. Svanteson M, Rollefstad S, Kløw NE, Hisdal J, Ikdahl E, Semb AG, et al. Associations between coronary and carotid artery atherosclerosis in patients with inflammatory joint diseases. RMD Open 2017;3:e000544.
22. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796–806.
23. Innala L, Möller B, Ljung L, Magnusson S, Smedby T, Södergren A, et al. Cardiovascular events in early RA are a result of inflammatory burden and traditional risk factors: a five year prospective study. Arthritis Res Ther 2011;13:R131.
24. Solomon DH, Reed GW, Kremer JM, Curtis JR, Farkouh ME, Harrold LR, et al. Disease activity in rheumatoid arthritis and the risk of cardiovascular events. Arthritis Rheumatol 2015;67:1449–55.
25. Aikawa E, Nahrendorf M, Figueiredo JL, Swirski FK, Shtatland T, Kohler RH, et al. Osteogenesis associates with inflammation in early-stage atherosclerosis evaluated by molecular imaging in vivo. Circulation 2007;116:2841–50.
26. Elnabawi YA, Dey AK, Goyal A, Groenendyk JW, Chung JH, Belur AD, et al. Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study. Cardiovasc Res 2019;115:721–8.
27. Døhn UM, Ejbjerg B, Boonen A, Hetland ML, Hansen MS, Knudsen LS, et al. No overall progression and occasional repair of erosions despite persistent inflammation in adalimumab-treated rheumatoid arthritis patients: results from a longitudinal comparative MRI, ultrasonography, CT and radiography study. Ann Rheum Dis 2011;70:252–8.
28. Smolen JS, Avila JCM, Aletaha D. Tocilizumab inhibits progression of joint damage in rheumatoid arthritis irrespective of its anti-inflammatory effects: disassociation of the link between inflammation and destruction. Ann Rheum Dis 2012;71:687–93.
29. Smolen JS, Han C, Bala M, Maini RN, Kalden JR, van der Heijde D, et al, for the ATTRACT Study Group. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the Anti–tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy study. Arthritis Rheum 2005;52:1020–30.
30. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al, for the ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006;295:1556–65.
31. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med 2011;365:2078–87.
32. Puri R, Nicholls SJ, Shao M, Kataoka Y, Uno K, Kapadia SR, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. J Am Coll Cardiol 2015;65:1273–82.
33. Räber L, Taniwaki M, Zaugg S, Kelbæk H, Roffi M, Holmvang L, et al. Effect of high-intensity statin therapy on atherosclerosis in non-infarct-related coronary arteries (IBIS-4): a serial intravascular ultrasonography study. Eur Heart J 2015;36:490–500.
34. Martín-Ventura JL, Blanco-Colio LM, Gómez-Hernández A, Muñoz-García B Vega M, Serrano J, et al. Intensive treatment with atorvastatin reduces inflammation in mononuclear cells and human atherosclerotic lesions in one month. Stroke 2005;36:1796–800.
35. Tawakol A, Fayad ZA, Mogg R, Alon A, Klimas MT, Dansky H, et al. Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multicenter fluorodeoxyglucose-positron emission tomography/computed tomography feasibility study. J Am Coll Cardiol 2013;62:909–17.
36. Einarsson JT, Willim M, Ernestam S, Saxne T, Geborek P, Kapetanovic MC. Prevalence of sustained remission in rheumatoid arthritis: impact of criteria sets and disease duration, a nationwide study in Sweden. Rheumatology (Oxford) 2019;58:227–36.
37. Hollan I, Dessein PH, Ronda N, Wasko MC, Svenungsson E, Agewall S, et al. Prevention of cardiovascular disease in rheumatoid arthritis. Autoimmun Rev 2015;14:952–69.
38. Evans MR, Escalante A, Battafarano DF, Freeman GL, O'Leary DH, del Rincón I. Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis. Arthritis Rheum 2011;63:1211–20.
39. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2006;113:30–7.